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MICROSTIMULATORS AND MICROTRANSDUCERS FOR FUNCTIONAL NEUROMUSCULAR STIMULATION

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Abstract

We are developing a new class of implantable electronic devices for a wide range of neural prosthetic applications. Each implant consists of a microminiature capsule that can be injected into any desired location through a 12 gauge hypodermic needle. Multiple implants receive power and digitally-encoded command signals from an RF field established by a single external coil. The first two types of implant that we have made were single-channel microstimulators equipped with either a capacitor-electrode or an internal capacitor that stores charge electrolytically and releases it upon command as current-regulated stimulation pulses. We are also working on implants equipped with bidirectional telemetry that can be used to record sensory feedback or motor command signals and transmit them to the external control system.

Long-Term Biocompatibility of Microstimulators

In an initial chronic biocompatibility study (see prior QPRs and Cameron et al., 1998), we reported that microstimulators implanted for 2-3 months in cats evoked modest foreign-body reactions similar to those produced by the concurrent implantation of negative control materials such as USP standard polyethylene rods and silicone tubes. We now report the results of an extended investigation of biocompatibility in which the tissue reactions to microstimulators were compared to microstimulators coated with a thin silicone sheath and to negative control materials in animals implanted for six and twelve month survival periods.

Six adult cats were used in the study. Each cat was anaesthetized with pentobarbital and implanted with three test and two control articles. One non-coated microstimulator was implanted into a tibialis anterior muscle, whereas the other four devices (coated microstimulator, non-coated microstimulator, silicone rod, USP standard polyethylene rod) were distributed in rostral and caudal parts of the lumbar paraspinal muscles bilaterally. The coated microstimulator was produced by expanding a thin-walled silicone tube (.075@ i.d. x .080@ o.d.) in heptane and then shrink-wrapping it onto the glass capsule of the microstimulator. The silicone rod was custom-fabricated from medical-grade silicone elastomer (Dow Corning MDX4-4210) to conform to the same external dimensions as the test articles. The polyethylene rod was obtained from a commercial testing laboratory and was cut to the same length as the test articles, but was smaller in diameter. Each device was inserted into a narrow perforation made into the muscle using sharp-tipped scissors. A 6-0 Ethibond suture was used to close the insertion site and reduce the possibility of device extrusion during the immediate post-operative period. Post-operative health status was monitored biweekly after the first week. The

temperatures, weights, food consumption and hematological status of the animals were evaluated and activity levels were assessed.

At the end of the prescribed survival period, animals were killed by an overdose of pentobarbital. A thorough whole-body necropsy of each animal was conducted by a qualified veterinary pathologist. The muscle around each implant was removed, the device was extruded and the tissue block was bisected through the center of the implant site. One block was fixed in formalin and was sent to a commercial research laboratory that embedded the blocks in paraffin and evaluated the cellular responses of the surrounding muscle. The other was frozen in nitrogen, sectioned and stained to demonstrate cellular morphology (H&E method) and ATPase activity on sequential sections. The biocompatibility of each device was assessed according to three criteria: the thickness of encapsulation around the device, the amount and type of inflammatory cell accumulation and the extent of fibrosis and muscle-fiber necrosis in the vicinity. Inflammatory cell scores were evaluated by a commercial testing laboratory (IDEXX, Sacramento, CA) according to standard protocols.

Of the six animals admitted initially to the study, five completed the entire trial uneventfully. These animals showed no detectable abnormalities in their health status, and demonstrated no detectable physical abnormalities at the time of necropsy. One animal that was admitted to the trial was recorded to have a distended abdomen that was attributed to fat at the time that the trial began. However, shortly after the beginning of the study the distension worsened and hematological testing revealed a dramatic drop in white-cell counts. The cat was diagnosed as having a fulminating uterine infection that responded poorly to antibiotic therapy. Thus the animal was withdrawn from the study, and subsequent necropsy revealed that the uterus was filled with inflammatory material and weighed in excess of a kilogram. The uterine infection was judged by the attending veterinarian to have been a preexisting condition evidenced by the large size of the

abdomen at the start of the trial, and was not believed to result from implantation of devices.

Analysis of muscle from the five animals that completed the trial showed similar tissue reactions to test and negative control articles (Figure1). The mean capsule thicknesses and cell scores around microstimulators, silicone rods or polyethylene rods were similar. However, the silicone rods and polyethylene rods had a tendency to migrate; one silicone rod and two polyethylene rods were retrieved from the fascia overlying the muscle. The reactions around the microstimulators appeared to bind the devices tightly to the connective tissues of the muscle. Thus when devices were removed at necropsy, the microstimulators did not extrude from the muscle easily as did the negative controls. Instead, connective tissues around the tantalum and iridium electrodes had to be cut in order to remove the devices, and histological evaluations showed an elaboration of non-reactive connective tissue emanating from the implant site amongst the muscle-fiber fascicles within a few hundred microns of the capsule (Fig. 2).

We conclude that the BIONs with and without silicone sheaths are mechanically stable and biomechanically compatible in active muscles for both short-term and long-term use.

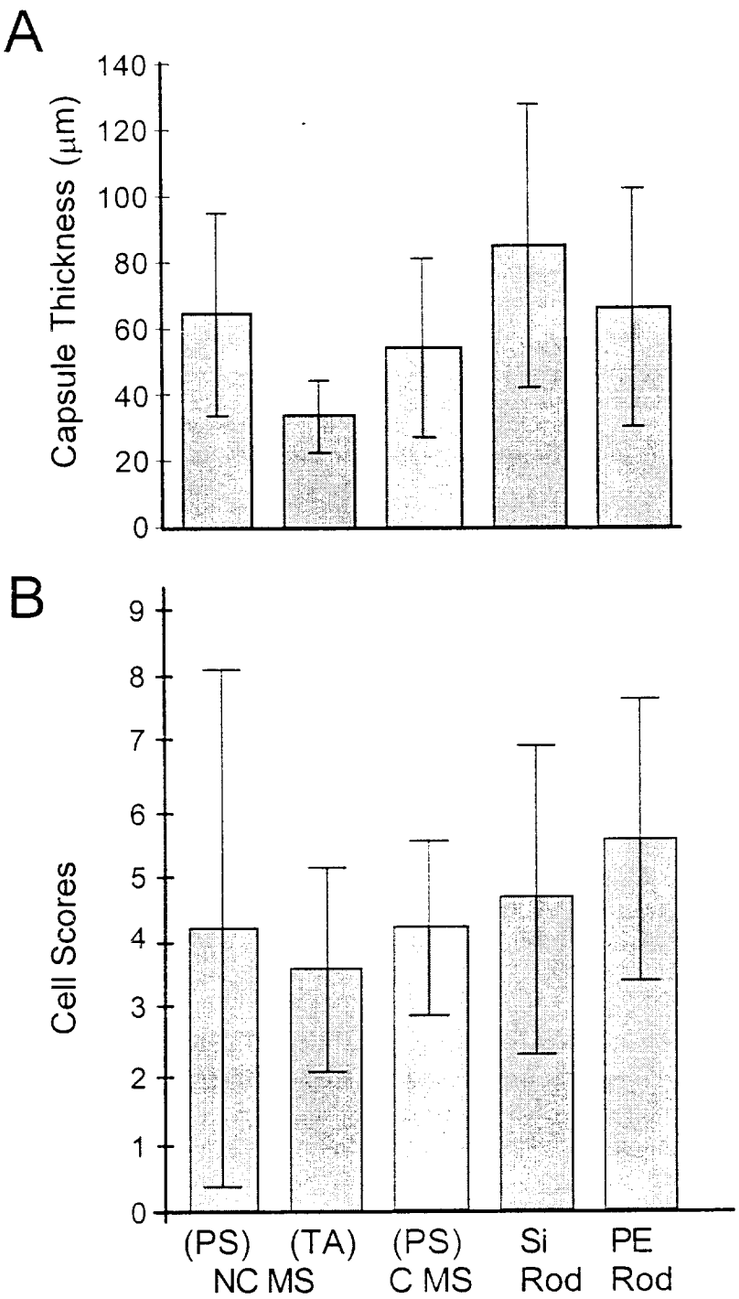

Figure 1. Capsule thicknesses (A) and cell scores (B) around non-coated microstimulators (NC MS), coated microstimulators (C MS) silicone rods (Si Rod) and USP standard plastic rods (PE Rod).

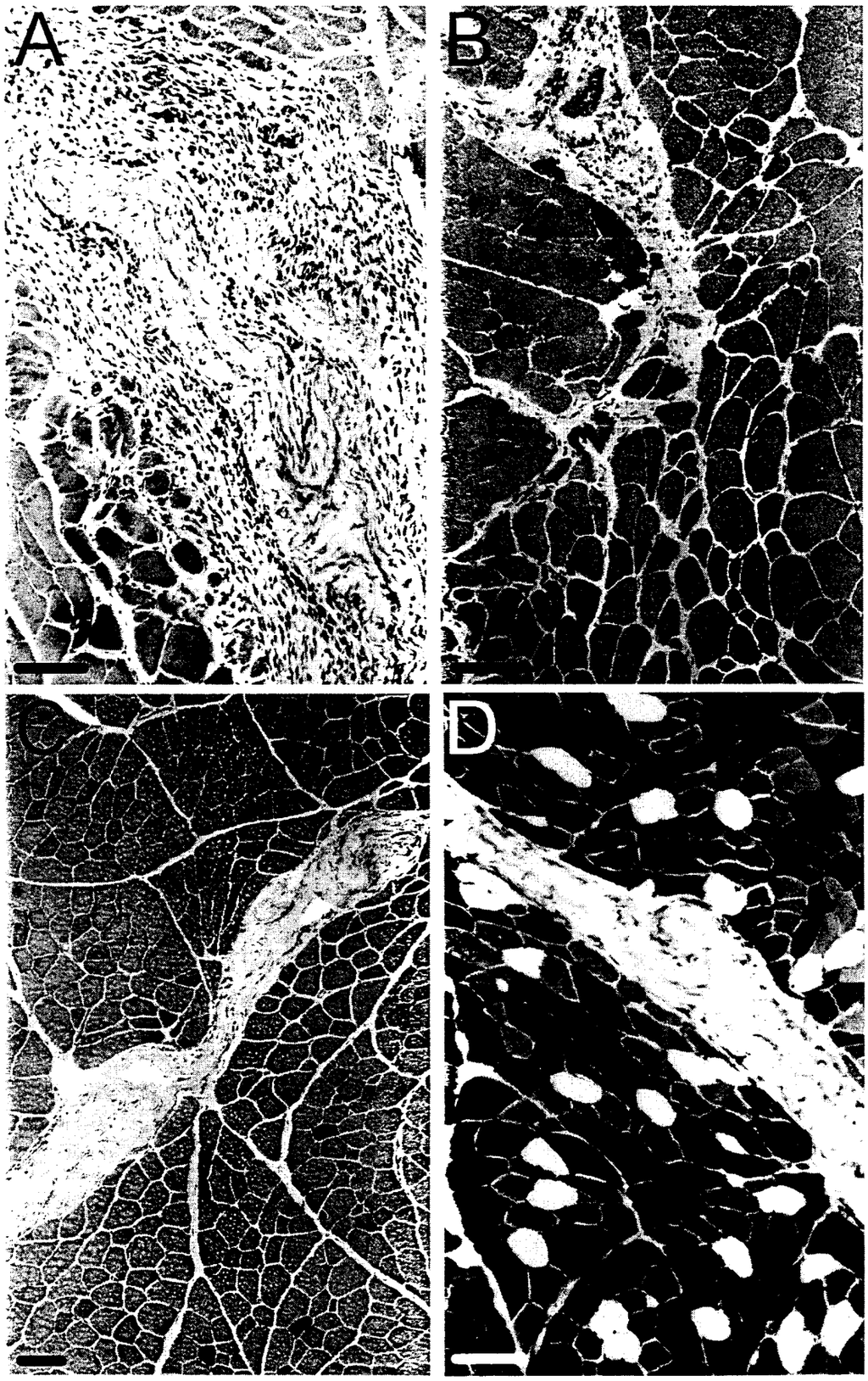

Figure 2: Histological appearance of capsules around test and control articles. Bars=100 microns

Encapsulation around a silicone rod, after a survival time of 6 months.

Note the presence of a dense flattened inner capsule and an elaboration of looser connective tissue around the implant site.

Fibrosis extending into interspaces around muscle fibers close to the site of implantation of a microstimulator, after one-year survival.

Capsule around a non-coated microstimulator. Note the flattened, thin nature of the collagen layers. Six-month survival.

Encapsulation around a non-coated microstimulator stained to demonstrate ATPase activity in tissue around the implant. Fibers around the implant site demonstrate morphologies and enzyme reactivities typical of normal muscle fibers elsewhere.

PRITZKER UNIVERSITY

Work at the Pritzker Institute

During the last quarter progress was made on the task of measuring the moisture content of sealed glass capsules.

We used impedance spectroscopy to measure the surface leakage across the interconnection traces on the ceramic substrate within the glass capsule. For these studies we used a modified bonding pattern on the ceramic substrate that permitted the connection of each side of a parallel track pattern to be electrically connected to the exiting electrodes; one side was connected to the iridium disk and the other side was connected to the tantalum slug. By using electrical contact clips on the electrodes, the impedance between the traces on the ceramic substrate could be measured prior to and following water-soak tests. By way of background, a brief description of the lateral impedance spectroscopy method is presented below.

Impedance Spectroscopy

Interdigitated metallized patterns have a long history of use for reliability testing of microelectronic polymer coatings [1,2,3,4,5,6]. Prior to this project, we had reported techniques for theoretical analysis [7] and laboratory measurement of D.C. leakage currents for interdigitated comb patterns. The conclusion of those studies is that present instrumentation techniques do not permit the measurement of D.C. leakage currents for interdigitated comb patterns which do **not** demonstrate interphase leakage orders of magnitude above that caused by the bulk polymer, or dry air. In other words, it is not possible to measure the D.C. interphase leakage for a sample in which there is little to no surface water.

Figure 1 shows the individual components which contribute to the leakage between two metal traces on a hypothetical substrate. The substrate impedance, Zsub,

and bulk polymer or dry air impedance, Zbulk, dominate the measured impedance under dry conditions. For a failed sample, the interphase impedance, Zinter, caused by the presence of water, dominates. For relatively thick polymer coatings, the contribution of the air, Zair, or even water above the polymer is negligible because it is in series with bulk polymer. For the these microstimulator samples, there is no polymer on the substrate. Therefore, under dry conditions, the surface impedance should be dominated by the substrate impedance in parallel with the impedance of the dry air.

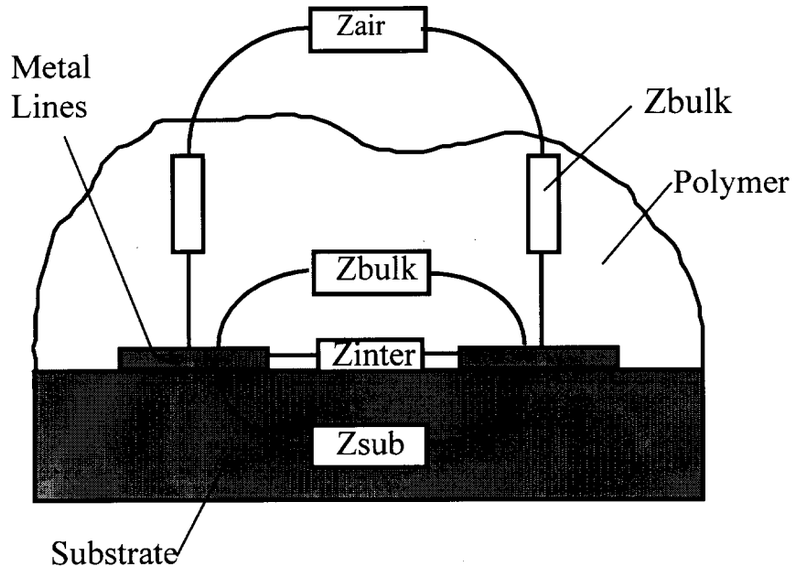

Figure 1 – Cross section of typical test pattern showing metal lines on an insulating substrate.

Although impedance spectroscopy has historically been extensively used for transverse impedance measurements, such as in paint coatings [8,9,10], there have been limited studies of interphase or lateral impedance measurements [11,12]. One can consider the lateral impedance measurement as an extension of the techniques used at D.C. The leakage current between the two halves of the pattern are measured over a range of frequencies, typically 0.001 Hz to 10 kHz. Many of the same instrumentation techniques which must be followed for D.C. leakage measurements are equally important for Lateral Impedance Spectroscopy. These are described elsewhere [13]. The advantage in using the LIS technique over D.C. leakage measurements lies in its ability to measure the interphase impedance in the absence of moisture, thereby providing a basis for evaluating moisture-induced conduction and subsequent device deterioration. In contrast, D.C. leakage measurements permit only the measurement of interphase leakage that is higher than a threshold dictated by instrumentation noise. Under dry conditions, LIS measures the Zsub in parallel with Zbulk, or Zair. Since the magnitude of these impedances is dominated by their dielectric constant, a typical "dry" impedance plot is a straight line, whose impedance rises by a factor of 10 for each drop in frequency. Under wet conditions, the presence of moisture alters the interphase impedance, Zinter, below that of the dry conditions, resulting in impedance curves that are characteristic of the presence of water.

Impedance Spectroscopy Results

Four glass capsules containing a ceramic substrate were sent to IIT in October of 1998. Testing began on 11/20/98 and has continued to the present day, 3/18/99.

The four sealed glass capsules were initially baked in an oven at 80 degress C for 48 hours. Following the bake-out, they were measured using impedance spectroscopy to determine the "dry impedance" curves of the internal substrates. Background impedance levels were determined by leaving the connection to the iridium electrode disconnected, but physically close to the electrode. Background impedance curves were found to be approximately 8-10 times those demonstrated by the dry glass capsules. Then, the capsules were soaked in 80 degree C water for 24 hours. Subsequently the impedance was measured again. No measurable difference was found between the dry and wet curves.

The glass capsules were left to continuously soak within the 80 degree C water. Impedance Spectroscopy measurements were made on 1/17/99 and 3/18/99. For all four capsules no measurable change in impedance was observed. Presently the samples remain soaking within the hot water.

Our conclusion is that these four samples show no significant leaks. By definition a significant leak is one that would cause increased electrical leakage due to the condensation of water on the internal substrate. In the absence of measurable surface leakage, no corrosion or deterioration of the internal electronic assembly would result. Furthermore, these capsules did not contain a moisture getter, so they represent a worst-case. Assuming that these four samples are representative of the population, one would

expect that identically-fabricated microstimulators would also exhibit no significant leaks.

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IMPROVED 2-MHZ MICROSTIMULATOR ASIC DEVELOPED

AT ALFRED E. MANN FOUNDATION

Dedicated Wafer Run

We received the first two wafers from the wafer run discussed in our previous report. (6 more wafers are being held pending any necessary changes.) One wafer has been sent out to thin it down to 200 microns to fit in the microstimulator package.

Initial testing of the improved microstimulators on the wafer indicates that they are fully functional as chips. The microstimulators in this wafer run are modified to provide longer pulses: The basic timing resolution is 2 μs, allowing pulses up to 510 μs to be generated. This modification performs as expected.

Testing of microstimulators on the wafers showed good yields, in excess of 90%. The first test assemblies using unlapped and uncoated chips, however, have shown relatively poor yields, on the order of 40%. We are working to identify the problem areas and modify the processing to improve the yields.

Among the chips included on the wafer run was a test chip for the suspended carrier front end (see page 9 of the 14th report). Due to a clerical error in the process of combining the chips onto one reticle, that test chip had open circuits at many of the pads, making testing of the chip essentially impossible. These opens and any other problems which can be fixed with metal layer changes will be corrected on the wafers which have been held in the early stages of processing.

As this report is being prepared for submittal, the corrections in the metal layers have been submitted for two more wafer releases.

Reliability and Qualifications

Approximately 20% of the bions fail during the assembly process. Accurate tracking procedures have been introduced to determine the precise points in the process where the failures occur. Protocols are being prepared for Qualification testing and for 100% process testing. An analysis to determine the causes of failure of these units is in progress.